



DEPARTMENT OF HEALTH AND HUMAN SERVICES

D1317B  
Food and Drug Administration  
Atlanta District Office  
HFI-35

60 8th Street, N.E.  
Atlanta, Georgia 30309

May 23, 1996

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Miguel Arteche, President  
Mikart, Inc.  
2090 Marietta Boulevard, NW  
Atlanta, Georgia 30318

**WARNING LETTER**

Dear Mr. Arteche:

An inspection of your drug manufacturing facility was conducted between April 16 and May 3, 1996, by Investigators Robert L. Lewis and Vincent M. Williams. This inspection was initiated to conduct a preapproval inspection associated with ANDA [REDACTED] USP and ANDA [REDACTED] USP. The inspection revealed several significant deviations from the Current Good Manufacturing Practice for Finished Pharmaceuticals (CGMPs), as set forth in Title 21 of the Code of Federal Regulations, Part 211. These deviations cause your generic drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

You have failed to establish and conduct an adequate stability testing program to assure that your drug products meet applicable standards of identity, strength, quality, and purity at their time of use. The investigators noted at least 200 stability samples scheduled to be analyzed between 4/4/95 and 12/31/95 which had not been completed by the analysts and/or reviewed by responsible quality assurance management. These samples comprise over 20% of the samples which were due to be analyzed in this time period. Included in these samples is Lot 930291C of Bancap HC capsules, which was to be tested in April 1995. The analysis of thirty of these samples had not even been initiated during the inspection. Included in this group of samples are Lots 940776 and 940777 of HBA Tablets, due to be tested in June 1995. An additional 57 stability samples were identified as not being completed and/or reviewed which were due to be tested between 1/1/96 and 2/28/96.

A review of the stability samples which had been tested revealed your firm's routine failure to test at the appropriate established intervals. Numerous instances of overdue testing (6-9 months late) were observed by the investigators. Failure to test at appropriate intervals defeats one of the primary purposes of the stability testing program, which is to detect quality problems in a timely manner so that Mikart can appropriately respond.

The tracking and documentation system for the stability program was clearly inadequate to monitor the volume of samples involved. It took your firm several days to determine the current status of many of these samples. The sample backlog and testing discrepancies illustrate that the stability testing program is not operating in an appropriate state of control at this time. It is of serious concern that Mikart may not have enough trained personnel to handle the current stability program.

An example of your firm's failure to adequately respond due to the above problems was noted in [REDACTED] USP, Lots 930807J and 930808J. The 18 month stability samples from these lots were tested 7 months late (one month beyond expiry date). Both lots were found to fail assay at that time. Your firm does not know at what point the lots became subpotent. A discrepancy report was not issued until three months after the testing and a failure investigation had not been initiated when our inspection began.

You have failed to adequately validate the manufacturing processes utilized to produce lots of Migrapap Capsules, USP. Significant changes were made to the blending process in September 1993 which were not appropriately evaluated by quality control. Four batches of product were released in 1994 which were manufactured utilizing this unvalidated process. Your firm attempted to concurrently validate this process in 1995 during the production of Lot B950184. This lot failed blend uniformity testing and the validation attempt was terminated. These four lots remained in distribution after your firm became aware that the manufacturing process was questionable. All lots were noted to have excessive rejects due to out of specification capsule weights during production. These lots were subjected to limited testing prior to release.

Another attempt was made to validate this product utilizing another manufacturing process approved in December 1995. Lot L951239 was manufactured as a validation lot in January 1996. The filling properties of the blend were found to be unsatisfactory and the incorrect manufacturing equipment was used. The validation study was cancelled but the lot was reworked and released for distribution. The reason given for this product release was that finished product testing did not indicate a problem. No amount of finished product testing would suffice to overcome the failure to validate the manufacturing process.

Your firm failed to adequately respond to failing analytical or out of specification test results. Two lots of Methazolamide Tablets with stability test failures were investigated 7 to 10 months later. Two lots of P-V Tussin Syrup with failing results in January 1996, have yet to be investigated. Inconsistencies were also noted in the recording of information on the failure investigation reports.

You have failed to validate the cleaning procedures in place at your firm. No validation studies for products other than liquids have been designed and test protocols have not been established. Acceptable residue limits have not been established for each product. This deviation was pointed out to Mikart in the previous inspection conducted in April 1995. Your firm's 5/15/95 response to that observation included a commitment to complete cleaning validation by 7/31/95.

Other significant deviations noted include no maintenance records for analytical equipment, deficiencies in employee training records, and deficiencies in water sanitization practices and procedures. Observations specific to the ANDA products under review included poor resolution of stability and finished product test chromatograms, failure to document mixing times or speeds for biobatches, and failure to test stability samples at appropriate intervals.

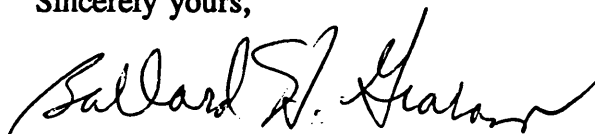
The above deviations were included on the extensive FDA 483 issued to and discussed with you at the conclusion of the inspection. The deviations discussed above and included on the FDA 483 should not be construed as an all inclusive list of violations which may be in existence at your firm. It is your responsibility to ensure adherence to each requirement of the Act. The violations noted in this letter and in the FDA 483 are symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems.

You are responsible for investigating and determining the causes of the violations identified by FDA. You should take immediate actions to correct these violations. Failure to promptly correct these deviations may result in legal sanctions provided by the law such as product seizure and/or injunction, without further notice to you. Federal agencies are advised of the issuance of all warning letters involving drugs so that they may take this information into account when considering the award of contracts.

Based on the significance of the investigators' observations during this inspection, we have recommended to the Center for Drug Evaluation and Research that approval be withheld for Mikart as a manufacturer for ANDA [REDACTED] and ANDA [REDACTED].

You are requested to notify this office within fifteen (15) days of receipt of this letter, of all the steps you have taken, or intend to take, to correct these violations. Your response should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead. This response should specifically address the concerns over the Migrapap lots which are still in distribution.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "Ballard H. Graham", with a stylized flourish at the end.

Ballard H. Graham, Director  
Atlanta District